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UPGRADING OF TECHNOLOGY IN INDIA FOR
THE EXTRACTION OF ALKALOIDS
FROM OPIUM

UC/IND/84/058

INDIA

Technical Report: Planning mission Phase I*

Prepared for the Government of India by
the United Nations Industrial Development Organization

Based on the work of Paul G. Mahlberg, expert in Industrial aspects of
production/processing alkaloids from opium

572

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TABLE OF CONTENTS

Cover page.....	1
Table of contents.....	2
Abstract.....	3
Introduction.....	4
Recommendations.....	5
I. Work carried out (Work Plan).....	7
1. Initiation of this programme.....	7
2. Organization of a Study Tour.....	8
3. Assessment of processing and production centers in India.....	10
4. Selection of laboratory for sample analysis.....	12
5. Market analysis.....	13
6. Initiation of discussions with the World Health Organization (WHO).....	14
II. Utilization of results from our study.....	15
III. Conclusions.....	16
IV. Time frame of WORK PLAN.....	17
Annexures (1-6).....	18-24

ABSTRACT

The objective of this United Nations Development Programme (UNDP) project, "Upgrading of Technology in India for the Extraction of Alkaloids from Opium (UC/IND/84/058 Rev. II)", is to improve and modernize the country's capabilities to manufacture opiate alkaloids and to expand both its national and international markets through the availability of diverse and purified products. A UNIDO consultant and national team of experts formulated a tour of pharmaceutical companies and international agencies in the United Kingdom, Federal Republic of Germany and Switzerland to obtain technological expertise for modernizing manufacturing facilities in India so as to produce purified alkaloids and derivatives. The national team will evaluate the present technology in India for processing opium. It selected the National Chemical Laboratory at Pune for alkaloid analyses and quality assessment of compounds now manufactured in India, and is evaluating both national and international markets for prospective sales of new products which could be manufactured in India with new technologies. These activities, components of Phase I, are to be completed in less than one year in preparation of Phase II which will lead to acquisition of new equipment and training of personnel to run a modern manufacturing factory and to expand marketing efforts for enhancing alkaloid sales. The Study Tour in Phase I is to learn new technologies for isolating and producing refined forms of alkaloids from opium, and to carry out a correlated marketing study for sales of these alkaloids in developed as well as developing countries.

INTRODUCTION

The project "Upgrading of Technology in India for the Extraction of Alkaloids from Opium" (UC/IND/84?058 Rev. II)" is a multifaceted effort to assist India to improve its manufacturing capabilities in the production of opium alkaloids and their derivatives. The programme will contribute to the establishment of modern manufacturing facilities and the incorporation of new technologies for implementing diversification in the production of opium products. The effort is recognized to be essential in the common interest both to maintain the cultivation of opium poppy as an agricultural crop in India and to provide world requirements of opium-based products for pharmaceutical and research purposes.

The immediate objective of this programme is to provide assistance to India to improve technology for the extraction of alkaloids from raw opium, the methylation of morphine into codeine, the ethylation of morphine into ethylmorphine, the manufacture of dihydrocodeine and pholcodine from morphine and hydrocodone, and the production of oxycodone from thebaine.

For this purpose I was sent to India as an international consultant during the period of November 24 to December 23, 1985 to initiate this programme with a group of Indian experts.

RECOMMENDATIONS

1. That the five Government of India nominations for the national team of experts be confirmed as members of the team, including Mr. M.C. Sharma (Project Coordinator), Mr. V. Kannan (Joint Project Coordinator), Mr. N.R. Ayyangar (Analytical Chemist), Mr. Rajiv Juneja (Marketing Expert), and Mr. S.P. Mukherjee (Processing Technologist).
2. That these same individuals compose the Study Tour team to visit companies and agencies in the United Kingdom, Federal Republic of Germany and Switzerland to obtain technological and related information on alkaloid production.
3. That the national team, prior to departure on the Study Tour, assess the present technology in India for processing opium and producing alkaloids of high purity. The team has begun to pursue this activity at the Neemuch and Ghazipur factories.
4. That the national team, prior to departure on the Study Tours, identify an appropriate laboratory in India for analyses and quality assessment of opiate alkaloids produced at their factories. The team has selected the National Chemical Laboratory at Pune and has begun evaluation of the products.
5. That the national team immediately begin a market analysis of opiate needs within India. This analysis is now in progress.
6. That the national team immediately begin a study to expand marketing of opiate products outside of India. The team has initiated this study for both developed as well as developing countries.

7. That the national team utilize the information gained from the above studies in planning the Phase II follow-up activities to carry out the development objective of the programme.

I. WORK CARRIED OUT

1. Initiation of this programme.

Shortly after my arrival the five members of the national team of experts and I met to outline the plans for implementing the programme to upgrade Indian technology and marketing capabilities in opium production. Members of the national team possess the appropriate expertise for this programme.

Mr. M.C. Sharma (Project Coordinator),

Mr. V. Kannan (Joint Project Coordinator),

Mr. N.R. Ayyangar (Analytical Chemist),

Mr. Rajiv Juneja (Marketing Expert),

Mr. S.P. Mukherjee (Processing Technologist).

I am serving as the international consultant with the national team.

This programme was initiated because of the accumulation of excess quantities of opium and alkaloid stocks in India, and the realization that present and future marketing of opiate products will require new approaches and directions if this industry is going to continue to prosper in India.

The cultivation and production of opium poppy (Papaver somniferum L.) is traditional in India and employs over 1 million labourers in states where it is grown. In response to increased world requirements in 1970s, India expanded its area under cultivation to the highest level of 63,700 hectares in 1978 which yielded 1,600 tonnes of opium. Since that time the demand for opium has decreased with the attendant decrease in area under cultivation to less than 30,000 h yielding about 900 tonnes of opium (1984). This downward trend has resulted in the loss of income for 75,000 families while another 170,000 have

suffered a partial loss of income. Any further reduction of agricultural area will have a major adverse socio-economic impact on a major industry in India, and it is essential therefore that opium production be stabilized at its present level.

However, even with the reduction in hectares of poppy cultivation an excess of approximately 2,200 tonnes of opium has accumulated between 1978 and the present time. A more appropriate figure is 1,800 tonnes since it is considered necessary to maintain approximately one year of production (700-900 tonnes) in reserve as a stock. However, the recent accumulation of excess opium is indicative of a future trend unless India upgrades its manufacturing technology and pursues new national and international markets.

2. Organization of a Study Tour

The national team of experts recognizes that alkaloid production facilities in India require modernization. We have prepared a plan to obtain the necessary technology for manufacturing facilities. During our meetings we evaluated companies for their technology in alkaloid production so as to select the most appropriate firms for visitation by the Study Tour team. Excellent technological capacity is represented by companies in the United Kingdom, Federal Republic of Germany and Switzerland, and we have selected several companies in each country. The companies and countries are listed in Annexure I.

Members of the national team are familiar with the leading personnel in these companies and are confident that these companies will be receptive of UNIDO requests for the Study Tour team to review their technological expertise. The names of individuals to contact in

these companies are included in Annexure I, and can serve as the initial contact for expediting the preparations of the Study Tour.

An itinerary of the Study Tour within the three countries has been prepared to assist UNIDO in planning the travel (Annexure 2). We have suggested calendar dates indicating the duration for each visit at a company--we believe this length of time will be adequate to acquire the desired information.

The month of May is suggested as the travel period since we realize that it will take UNIDO several months from the date of this report to complete all arrangements for the visitations. However, the departure date is flexible, and the Study Team would like to commence the study as soon as possible.

If UNIDO is unable to obtain company approval for a visit, that company can be removed from the list and the duration of the tour appropriately shortened.

As the international consultant I place a high priority on accompanying the group during the last week of the tour for visits to companies in Switzerland, to WHO, and then for the discussion with the team at UNIDO in Vienna. The team requested that I be with them at other times during their tour; I could consider the first week as a possibility (see Time Frame of Work Plan).

The rationale for visiting these companies is as follows: in the United Kingdom, Macfarlan Smith Ltd. for hydrocodone technology, the May & Baker Ltd. for pholcodine expertise, and the Boots Co. for noscopine technology. In West Germany, each of the companies (Boehringer, Merck, Goedecke, Hoffman-LaRoche, Knoll) have their own processes for isolating and purifying alkaloids and manufacturing

derivatives. Importantly, they have the technology for the conversion of morphine to codeine. We will visit each company to obtain comparative information on their technology so as to evaluate which process will be appropriate for development in India. In Switzerland we will gain the very important technological information from Knoll A.G., Sandoz Ltd., and Zyma on the isolation and purification of noscopine from opium, and its conversion to derivatives as tritoqualine. Although some companies, as Sandoz Ltd., no longer process opium they do possess the technological expertise, and are willing to share it with us.

During the Study Tour the marketing experts will review the markets in developed countries for specific opiate alkaloids and their derivatives. They will assess the potential of expanded sales of alkaloids produced with modernized manufacturing facilities using the new technologies when they become available in India. The marketing potential also will be discussed with appropriate World Health Organization (WHO) personnel in relation to the marketing of opiate products in developing countries under the WHO Action Programme on Essential Drugs (See 6).

3. Assessment of processing and production centers in India.

The national team currently is assessing the opium production and manufacturing facilities in India. Members met at the Neemuch site while I was in India. They will continue to visit both the Neemuch and Ghazipur factories to familiarize themselves with these facilities prior to beginning their Study Tour of European companies. Thus, they will have a basis for recognizing the technological requirements for

these two factories.

The team is aware that present facilities are inadequate compared to those in manufacturing companies elsewhere. Its evaluation of the status of national facilities will provide the basis for selecting the technologies appropriate for India's future needs so as to make India competitive in producing refined and diverse opiate alkaloids for world markets.

The Government of India Opium & Alkaloid Works Undertaking maintains opium processing facilities at two locations, Neemuch and Ghazipur. The factory in Neemuch was established in 1976 and consists of two units, the opium factory and the alkaloid plant. The Opium factory was formed in 1935. While the factory was of modern design when built in 1976, it has not kept pace with development of new technologies. As a result the manufacturing capabilities at this plant are now limited for the production of refined alkaloids, salts, and derivatives to meet the demands of the market.

The Alkaloid Works Undertaking in Ghazipur is much older than at Neemuch. The city of Ghazipur is associated with the traditional production of opium in India. In 1943, a small alkaloid plant was built at the much older opium factory to meet India's military needs during World War II. Few changes have occurred at these facilities since that time. Unlike at the Neemuch Research & Development section, the Ghazipur facility is not well equipped nor does it possess modern instruments. Thus, it performs a limited role in alkaloid production compared to the Neemuch facility.

The national team recognizes the production capacities and limitations of these two facilities. It attaches importance to the

planned Study Tour of manufacturing companies in Europe with the objective of transferring new manufacturing technologies to this country. It is planned to upgrade the facilities and technology at both existing factories, with priority placed upon the facility at Neemuch. However, we realize that new technologies must be developed at both factories, each initially specialized in the manufacture of specific alkaloids and derivatives, to provide adequate quantities for the new marketing programme.

4. Selection of laboratory for sample analysis.

The national team has selected the National Chemical Laboratory at Pune to perform quality analyses of opiate alkaloid samples manufactured at the two factories. The laboratory is equipped with modern and appropriate instrumentation to perform the analyses and assess the quality of products now produced in India. These data will be at hand with the Study Tour so that members can discuss this information with personnel at manufacturing companies in Europe.

Analyses on representative samples will begin immediately. Since the laboratory now routinely performs analyses on various alkaloids the Study Tour members will have all the necessary analyses completed while UNIDO makes arrangements for the trip. This information will assist members in comparing the procedures employed elsewhere for isolating and purifying individual alkaloids, evaluating the cost effectiveness of different procedures to prepare different alkaloids of high quality, and for the manufacture of salts and derivatives.

5. Market analysis.

The national team recognizes that India must acquire modern facilities to prepare highly purified products for markets. Its present manufacturing facilities do not meet the standards of those in companies of developed countries. Therefore, India cannot compete in the marketing of opiate products compared to those produced by foreign companies. The team has undertaken a review of the products consumed in developed countries and realizes that India can gain a major share of these markets if these products can be produced here.

A marketing survey has been initiated by the team and will continue until its departure on the Study Tour. The potential for new markets of refined products is illustrated for non-producing countries. Significant quantities of hydrocodone and oxycodone are currently consumed (Table 1), also pholcodine (Table 2), and ethyl-morphine (Table 3). A broad potential market for highly purified codeine and dihydrocodeine exists among non-producing nations (Table 4), and among manufacturing countries as well, if Indian can produce these products competitively. Similarly, an increasing demand in Japan and elsewhere for noscopine and its derivatives represents an excellent market for India if it possessed the technology to manufacture these products.

The information from these analysis of existing markets is to be utilized for planning and selecting the appropriate technologies to be developed in India.

6. Initiation of discussions with the World Health Organization (WHO).

Mr. Kannan and I visited with Dr. B.B. Gaitonde of WHO in Delhi to initiate an assessment of potential markets in developing countries, particularly the countries of Africa. The basis for this inquiry relates to reports that consumption of opiate pharmaceuticals in developing countries is estimated at only 30% of actual needs. Factors influencing potential needs include dependence on folk medicines, difficulties of foreign exchange, lack of adequately complete surveys on use of opiate-based products and general unavailability of opiate-based products for anti-tussive, analgesic, and anti-diarrhetic medication.

Dr. Gaitonde recommended that the Study Tour members discuss this topic with WHO representatives in Geneva. He emphasized that the WHO in Delhi serves only countries of the south east Asia area, and that there is no programme to assist for surveying needs in pertinent countries nor financial support for the production or distribution of such preparations through the Delhi office.

The Study Tour team has included visitation with members of WHO in Geneva in its itinerary (Annexure 2). There we will initiate discussions on how WHO could assist in making codeine-based preparations available for developing countries through the WHO Action Programme on Essential Drugs. If it is ascertained that the needs for these pharmaceuticals are not being met in these countries because of conditions beyond their control, this would be a basis for recommending further examination of a plan to provide a supply of codeine pharmaceuticals to these countries under a subsidized or

cost-free condition. We do not suggest that medical needs of these countries should be correlated with the excess stocks of opium. However, if WHO upon assessment of medical needs in these countries found a valid need to organize such a programme, it would absorb a portion of the excess stock while satisfying the medical requirements of other countries.

II. UTILIZATION OF RESULTS FROM OUR ACTIVITY

My role as a consultant to the national team of experts was to assist members of this team formulate ideas reflective of experience outside India. With this point in mind for Phase I of this programme we assessed the present technological capacity for alkaloid production, we organized plans for a Study Tour to pertinent companies with desired technologies in the manufacture of alkaloids, we initiated an assessment of potential markets for particular alkaloids as well as initiated contact with WHO for further inquiry into potential markets in developing countries.

Information to be gained from activities carried out prior to the Study Tour and from visits to companies and agencies during the Tour will be utilized to formulate a Phase II for this programme. The second phase will include the acquisition of equipment for upgrading alkaloid manufacturing and processing technology, and to carry out training programmes in the areas of production, processing and marketing.

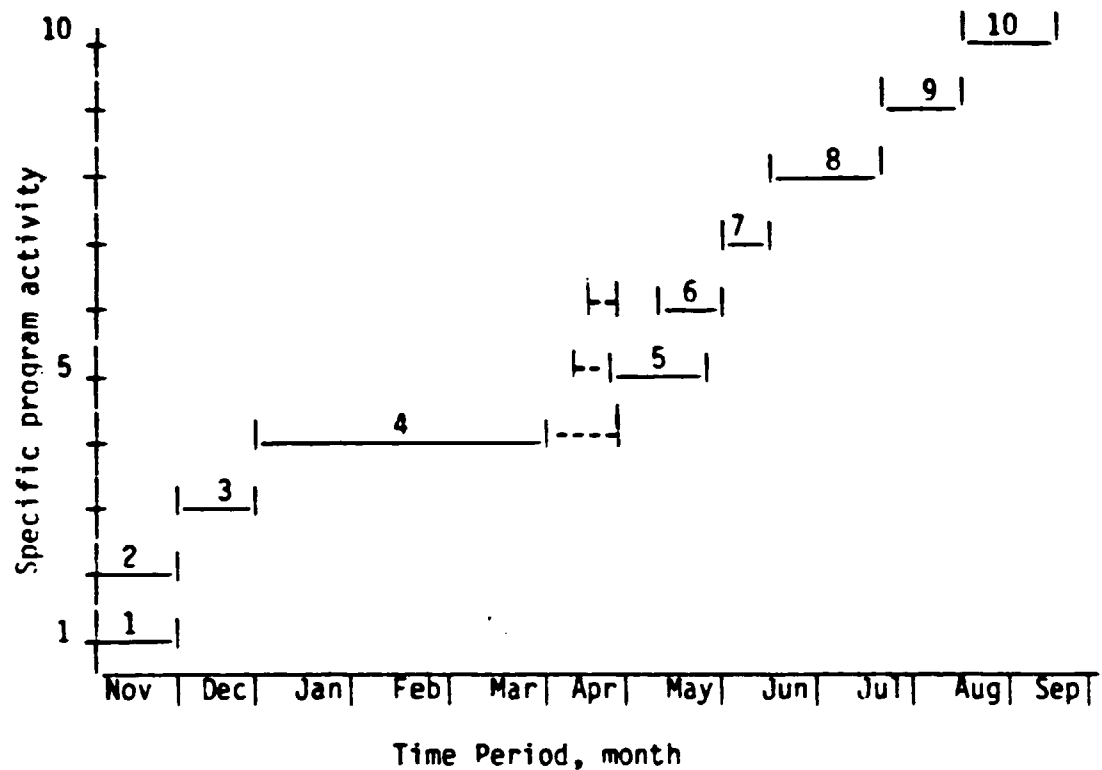
The principal factor that will affect Phase II will be economic

in character. The modernization of factory facilities will require the investment of money for the purchase of equipment, possibly the construction of physical facilities, and the training of personnel to operate and manage the technologically advanced facilities as well as to market the products. Thus, Phase II will be critical to implementing the desired upgrading of opium manufacture in this country.

III. CONCLUSION

Our efforts to formulate a Phase I of this programme have been successful. I anticipate that members of the group will obtain the desired information during the Study Tour. It will be their role to use this information to formulate Phase II of the programme and gain the financial support to develop modern manufacturing facilities in India.

IV. TIME FRAME OF WORK PLAN



1. Nomination and constitution of Indian team of experts.
2. Selection of international consultant.
3. Development of WORK PLAN.
 - a. Itinerary of Study Tour.
 - b. Initiation of market analyses.
 - c. Selection of national laboratory for product analyses.
4. Initiation of work of national team.
 - a. Visit Indian factories
 - b. Analyses of representative samples
 - c. Prepare marketing analyses.
5. Study Tour of Indian team of experts.
6. Consultant traveling with Study Tour team.
7. Discussions of team with UNIDO in Vienna.
8. Finalization of report by Coordinator of Study team.
9. Assessment of report by UNIDO and consultant.
10. Vienna for discussions on draft of final report, and initial planning of PHASE II.

Annexure 1

COMPANIES TO BE VISITED

	<u>United Kingdom</u>		<u>Telex</u>
1.	M/s. Macfarlan Smith Ltd. Wheatfield Road Edinburg, EH-2QA	Mr. Marshall Smalley, Managing Director Mr. Ron Waugh, Purchasing Manager Tele: 031-3372434	727271
2.	M/s. May & Baker Ltd. Dagenham Essex RM10 7XS, England	Mr. W.P. Franklin Materials Manager Tele: 01-592-3060 Extn. 3789	28691
3.	M/s. The Boots Co. PLC (Purchasing Dept.) Station Street Nottingham NG 2 3AA	Mr. Stewart Pierce Chief Purchasing Mgr. Mr. N.J. Ball Raw Material Buyer Tele: (0602)56255	377811
	<u>West Germany</u>		
1.	M/s. Boehringer Ingelheim KG (6507) Ingelheim AM Rhein, Abteilung Einkauf.	Mr. Harald H. Becker Mr. Jupp Pink Tele: 771-06132	41879123 bid
2.	M/s. E. Merck Postfach 4119 6100 Darmstadt 1 Frankfurter strabe 250	Mr. Wilhelm Schmitt Tele: (061 51) 72-1	419328-0
3.	M/s. Goedecke Ag. 7800 Frieburg Postfach 569 Meeswaldallee 1-9, Berlin	Mr. R. Rochus Tele: (0761)5-111 (07624)14-290	0772879
4.	M/s. Hoffmann-La Roche AG D-7889 Grenzabh Wyhlen	Mr. Machran H. Schmitt Tele: (07624)14-1 (07624)14-290	773174
5.	M/s. Knoll AG Knoustr 250 6700 Ludwigshafen		

Annexure 1 (continued)

Switzerland

- | | | |
|--|---|--------|
| 1. M/s. Knoll A.G.
C.H. 4410, Liestal
Postfach 631 | Mr. W. Viertel
Chief Executive
Tele: (061)912505 | 966000 |
| 2. M/s. Sandoz Ltd.
Purchasing Dept.
CH-4002 Basle,
Switzerland | Mr. W. Schweizer
Chief Executive
Tele: (061)241111
(061)240011 | 63163 |
| 3. M/s. Zyma (CIBA GEIG)
CH-1260 NYON
ZYMA SA 1260 NYON
Switzerland | Mr. Lucien M. Pigoet
Manager Purchasing Dept.
Tele: (022)6361111 | |

Annexure 2

PROPOSED TOUR PROGRAM FOR UNIDO TEAM

May 3 Saturday	Lv. Delhi, arr. Frankfurt
May 4 Sunday	Leave for Freiburg
May 5 Monday	Goedecke, Freiburg
May 6 Tuesday	
May 7 Wednesday	
May 8 Thursday	Hoffmann-La Roche, Myhien
May 9 Friday	Knoll AG, Ludwighafen
May 10 Saturday	
May 11 Sunday	
May 12 Monday	
May 13 Tuesday	Boehringer, Ingelheim
May 14 Wednesday	Boehringer Ingelheim
May 15 Thursday	E. Merck, Darmstadt
May 16 Friday	E. Merck, Darmstadt
May 17 Saturday	Leave for U.K., London (Arr.)
May 18 Sunday	London
May 19 Monday	Boots Ltd., Nottingham
May 20 Tuesday	Boots Ltd., Nottingham
May 21 Wednesday	May & Baker, Dagenham
May 22 Thursday	May & Baker, Dagenham
May 23 Friday	London
May 24 Saturday	Leave for Edinburg
May 25 Sunday	
May 26 Monday	Macfarlan Smith, Edinburgh
May 27 Tuesday	Macfarlan Smith
May 28 Wednesday	Travel to London or way to Zurich
May 29 Thursday	Knoll A.G., Zurich
May 30 Friday	Knoll A.G., Zurich
May 31 Saturday	
June 1 Sunday	
June 2 Monday	Sandoz, Basle
June 3 Tuesday	Sandoz, Basle
June 4 Wednesday	Zyma Ciba Geigy, Nyor
June 5 Thursday	Zyma & Travel to Geneva
June 6 Friday	WHO, Geneva
June 7 Saturday	Geneva
June 8 Sunday	Leave for Vienna
June 9 Monday	Vienna
June 10 Tuesday	Vienna
June 11 Wednesday	Return to Delhi

Annexure 3

Table 1. Hydrocodone and oxycodone consumption in countries not Manufacturing these compounds.

Country	Annual consumption, Kg	
	Hydrocodone	Oxycodone
Belgium	30	2
Bolivia	2	-
Bulgaria	2	-
Canada	150	90
Columbia	-	55
Finland	-	10
Greece	30	-
Guatemala	2	-
India	12	-
Israel	-	3
Mexico	30	4
Nicaragua	4	-
Peru	25	-
Phillipines	35	-
Poland	-	3
Sweden	-	2
Switzerland	1	-
Total	333	160

Annexure 4

Table 2. Pholcodine consumption in countries not manufacturing this compound.

Country	Annual consumption, Kg
	Pholcodine
Algeria	65
Bangladesh	25
Finland	6
India	50
Malaysia	7
Morocco	123
New Zealand	93
Pakistan	150
Singapore	4
Sweden	11
Switzerland	137
Tunisia	23
Zambia	30
Zimbabwe	1
Total	<u>725</u>

Annexure 5

Table 3. Ethylmorphine consumption in countries not manufacturing this compound.

Country	Annual consumption, Kg
	Ethylmorphine
Afghanistan	2
Albania	2
Austria	4
Brazil	90
Cuba	60
Denmark	10
Egypt	25
Finland	75
German Democratic Republic	8
Morocco	88
Sweden	200
Venezuela	80
Total	639

Annexure 6

Table 4. Codeine and dihydrocodeine consumption in countries not manufacturing these compounds.

Country	Annual consumption, Kg	
	Codeine	Dihydrocodeine
Argentina	270	-
Austria	-	137
Brazil	2,200	-
Chile	91	-
Columbia	52	29
Cuba	350	-
El Salvador	52	-
Ecuador	-	23
Egypt	-	40
German Democratic Republic	-	5
Ghana	41	-
Guatemala	34	8
Korea	-	450
Malaysia	-	73
Mexico	504	-
Portugal	-	6
Venezuela	176	5
Zimbabwe	-	1
Total	3,780	777